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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/753,750	11/29/96	LO R	63637-0102

EXAMINER

HM21/0612

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ART UNIT	PAPER NUMBER
~~MACKEY, K~~ 1645	9

DATE MAILED: 06/12/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 3-2-98

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), ~~or thirty~~ days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-4, 8, 10, 12, 14, 20, 28 ~~is~~/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-2, 3, 4, 8, 10, 12, 14, 20, 28 ~~is~~/are rejected.
☒ Claim(s) _____ is/~~are~~ objected to.
☒ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. The amendment filed 3/2/98 (paper no. 8/B) has been received and entered. Claims 1-4, 8, 10, 12, 14 and 28 are pending in the application.

2. Applicant's election with traverse of Group I, claims 1-4, 8, 10, 12, 14 and 28 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that claims relate to transferrin binding proteins of *Pasteurella haemolytica*, the examination of the entire application is not serious burden on the examiner to examine all claims together. The arguments have been fully considered but are not found to be persuasive. MPEP 803 states that restriction is proper between patentably distinct inventions, where the inventions are independent or distinct as claimed and there is serious burden on the examiner if restriction is not required. The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each other. In the instant situation, Inventions I (or II), III (or IV), and V (or VI), are distinct products, with different chemical structures and different biological properties (i.e immunogenicity), and inventions III (or IV) and VII are related as product and processes of use which are related as separate products capable of separate manufacture, use or sale as described in the previous office action. Restrictions between the inventions is deemed to be proper for the reasons previously set forth. A burden exists in the examination of these inventions. MPEP 803

states that a burden can be shown if the examiner shows either separate classification, separate status in the art or a different field of search. In the instant case a burden has been established in showing that the inventions of Groups I-VII are classified separately necessitating different searches in the U.S. Patent shoes. Additionally, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Further, it is submitted that the inventions of Groups I-VII have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

3. Claims 1-4, 8, and 10 remain rejected under 35 U.S.C. 102(b) as being anticipated by Murphy et al.

Applicants argue that Murphy et al did not disclose a purified and isolated nucleic acid molecule encoding a transferrin binding protein. Murphy et al do not provide guidance to isolate a gene encoding a transferring binding protein from the DNA crudely isolated from *Pasteurella haemolytica*. A product claim is not anticipated unless each element of the claimed product is disclosed in a single reference and the reference provides a method of making the claimed product.

Applicants' arguments have been fully considered but not found to be persuasive because Murphy et al disclosed isolation and purification of total cell DNA from *Pasteurella hemolytica*

and hybridization with a probe (see p. 2304 para 1-3; fig. 1) which is a naturally occurring nucleic acid molecule inherently contains complementary sequences, inherently encodes a transferrin binding protein and capable of hybridizing under stringent hybridization conditions. Even though Murphy et al did not disclose the term a transferrin binding protein, claims read over prior art because applicants claiming an isolated and purified nucleic acid molecule encoding a transferrin binding protein without identifying any SEQ ID NO: (Murphy et al disclosed such a molecule) which inherently encodes a transferrin binding protein and furthermore, a transferrin binding protein has not been characterized or identified in claim 1 such as molecular weight of the protein. Applicants merely claiming a transferrin binding protein which could be any protein molecule in the absence of characterization of protein. Recitation of a naturally occurring nucleic acid molecule, hybridization under stringent hybridization conditions and at least 15 contiguous bases of unspecified SEQ ID NO:, a fragment and complement, all are disclosed by Murphy et al. Although SEQ ID NO:1 or seq 80% homologous thereto in claim 4, is not disclosed but claim reads over prior art because the chromosomal DNA disclosed by Murphy et al inherently encodes the claimed seq and thus it meets the structural requirement of claim 4. Each element of these claims is disclosed by Murphy et al contrary to the assertion of the applicants.

4. Claims 1-4, 8, 10 and, 12, 14, 20 and 28 remain rejected under 35 U.S.C. 103 as obvious over Murphy in view of Loosmore et al.

The teaching of Murphy et al is set forth above which teaches isolation and purification of total cell DNA from Pasteurella hemolytica and hybridization with a probe (see p. 2304 para 1-3; fig. 1) which is a naturally occurring nucleic acid molecule inherently contains complementary sequences, inherently encodes a transferrin binding protein and capable of hybridizing under stringent hybridization conditions. Murphy et al does not teach cloning, expression of transferrin binding protein and a vaccine.

Loosmore et al teaches cloning, hybridization under stringent hybridization conditions, expression of a transferrin binding protein and use of said recombinant expression vector as a vaccine in a pharmaceutically acceptable carrier for the treatment of Haemophilus infection (see abstract; p. 7 lines 4-35, p. 9, lines 1-15, examples 2-21; summary of the invention p. 67, claims and entire document). Loosmore et al teach a recombinant expression vector comprising a nucleic acid molecule and transcription and translation elements operatively linked to the nucleic acid molecule (see examples 19-21, 8-10) because without these elements protein cannot be expressed. Loosmore et al teach a nucleic acid molecule which encodes a transferring binding protein from Haemophilus which is considered to be a homologous sequence of SEQ ID NO:1

It would have been obvious to one of ordinary skill in the art at the time of invention was made to purify and isolate nucleic acid molecule encoding a transferrin binding protein of Pasteurella hemolytica and express, hybridize, prepare oil go and use recombinant molecules as vaccine in a pharmaceutically acceptable carrier as suggested by Loosmore et al. One would have been motivated to do so because this is within the level of one of ordinary skill in the art to simply

substitute routinely used procedures performed by Loosmore et al for a transferrin binding protein from Haemophilus to another bacterial pathogen Pasteurella hemolytica of Murphy et al because both the organisms share and/or expected to have sequence homology. The invention as a whole is prima facie obvious.

Applicants argue that Murphy et al did not disclose or suggest the sequence or identification of a transferrin binding protein. There is no disagreement. Applicants argue that nucleic acid sequences of Pasteurella haemolytica only share 40% homology with the Haemophilus sequences described By Loosmore. Applicants did not use any of the sequence information provided in Loosmore et al to obtain their claimed nucleic acid molecules. There is greater than 85% amino acid identity among the TbpA proteins from Pasteurella haemolytica, there is only 40% homology between the TbpA sequence of Haemophilus influenza and Pasteurella haemolytica. Due to poor sequence identity between the genes between two organisms, the Haemophilus transferrin genes would not be useful as probes to isolate nucleic acid molecules encoding transferrin binding proteins from Pasteurella. Applicants also argue that applicants did not utilize the antibody screening method of genes as set forth by Loosmore et al but used PCR techniques to amplify the genes from Pasteurella using amino acid sequence determined by the applicants.

Applicants' arguments have been fully considered but not found to be persuasive because first 40% sequence homology is sufficient to isolate the gene as claimed under stringent hybridization conditions. Second, it does not matter which techniques applicants use to isolate the

nucleic acid molecules, the end product will be same. Loosmore et al provides motivation to one of ordinary skill in the art to isolate the claimed gene because Loosmore et al teaches all the elements of the claims except organism Pasteurella haemolytica. One of ordinary skill in the art can easily isolate the claimed gene from another organism given the facts that Loosmore et al provides all the reagents and tools necessary to isolate the claimed nucleic acid molecule.

5. Claims 4, 8 and 10 remain rejected under 35 U.S.C. 112, second paragraph for the reasons set forth in the previous office action.

Applicants argue that the term "homologous" is described on page 9, lines 13-21. The arguments are not persuasive because no guidance has been provided to calculate sequence homology between two sequences. Applicants' arguments are non-responsive to "at least 80% homologous". Applicant should note that a percentage of sequence homology/ identity is meaningless in the absence of mathematical algorithm and parameters employed to calculate such number. Depending on the gap weight, gap length, lengths of two sequences to be compared, etc., a percentage of sequence identity can vary.

Applicants' arguments in regard to "stringent hybridization conditions" on page 9, lines 25-31, are not persuasive because the specification states that appropriate stringent hybridization conditions are known to one of skilled in the art and state variable salt concentrations and temperatures therefore, it is still not clear which stringent hybridization conditions applicants intend to claim.

Applicants did not present any arguments for the recitation of "complementary", and "a fragment".

Claims 12, 14 , 20 and 28 rejected under 35 U.S.C. 112, second paragraph, has been withdrawn in view of amendment of claim 12.

6. Claims 1-2, 12 and 20 remain rejected under 35 U.S.C. 112, first paragraph for the reasons set forth in the previous office action.

"One cannot apply the teaching of specification from one example to get other variants, in the absence of such information one of skill in the art would not be able to obtain, or predict how to modify and retain the structural and biological properties of, all of the transferrin binding polypeptides as a vaccine for the prophylaxis and treatment of an infection caused by a Pasteurella spp encompassed in the claims without undue experimentation. Indeed, on p. 55-56, lines 10-12 of the specification, applicant states that vaccination with Tbp1 alone was of no benefit after experimental challenge therefore, it is unpredictable in the art ------".

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khalid Masood whose telephone number is (703) 305-6998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 308-4242. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

If attempts to reach the examiner by telephone are unsuccessful, the examiners's supervisor, Dr. Paula Hutzell, can be reached on (703)308-4310.

Khalid Masood, Ph.D.

May 12, 1998

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER